Clinical trial results:
Randomized, double-blind, parallel group, placebo-controlled, dose finding study in colorectal cancer patients receiving 5-FU-based chemotherapy to assess the efficacy of different doses of s.c. elsiglutide in the prevention of Chemotherapy Induced Diarrhea (CID)

Summary

EudraCT number	2014-000998-39
Trial protocol	DE HU CZ BG
Global end of trial date	09 February 2016

Results information

Result version number	v1 (current)
This version publication date	01 April 2017
First version publication date	01 April 2017

Trial information

Trial identification

Sponsor protocol code	TIDE-13-22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02383810
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 73491

Notes:

Sponsors

Sponsor organisation name	Helsinn Healthcare SA
Sponsor organisation address	Via Pian Scairolo 9, Lugano/Pazzallo, Switzerland, 6912
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the efficacy of 3 subcutaneous (s.c.) doses of elsiglutide vs. placebo and vs. each other in the prevention of chemotherapy-induced diarrhea (CID) in colorectal cancer patients treated with 5 fluorouracil (5-FU)-based chemotherapy (FOLinic acid, Fluorouracil, OXaliplatin [FOLFOX] or FOLinic acid, Fluorouracil, IRInotecan [FOLFIRI regimen]) with no addition of a monoclonal antibody.

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in the 59th World Medical Association Assembly, Seoul), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines .

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	Belarus: 31
Country: Number of subjects enrolled	Ukraine: 209
Country: Number of subjects enrolled	Russian Federation: 182
Worldwide total number of subjects	498
EEA total number of subjects	76

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	331
From 65 to 84 years	167
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	538[1]
Number of subjects completed	498

Pre-assignment subject non-completion reasons

Reason: Number of subjects	exclusion criteria met in the Screening period: 1
Reason: Number of subjects	Randomization not within protocol visit window: 1
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Consent withdrawn by subject: 18
Reason: Number of subjects	Inclusion/Exclusion criteria not met (cycle 1): 19

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Overall, 538 subjects were screened, a total of 498 subjects were randomized into the study ; 40 subjects were screen failures

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Placebo and active treatments were identical in appearance. To cover the double-blind, double-dummy design, the daily administration for each of the 4 treatment groups was of 4 vials of study treatment in total including up to 4 vials of placebo in total.

Arms

Are arms mutually exclusive?	Yes
Arm title	Elsiglutide 10 mg - target population

Arm description:

Elsiglutide 10 mg once daily as subcutanous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy

Arm type	Active comparator
Investigational medicinal product name	Elsiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 10 mg/day elsiglutide.

Arm title	Elsiglutide 20 mg - target population

Arm description:

Elsiglutide 20 mg once daily as s.c. injection for 4 consecutive days in patients receiving F-FU based chemotherapy.

Arm type	Active comparator
Investigational medicinal product name	Elsiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 20 mg/day elsiglutide.

Arm title	Elsiglutide 40 mg - target population

Arm description:

Elsiglutide 40 mg once daily as subcutanous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

Arm type	Active comparator
Investigational medicinal product name	Elsiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 40 mg/day elsiglutide.

Arm title	Placebo - target population

Arm description:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

Arm title	Elsiglutide 10 mg - additional population

Arm description:

Elsiglutide 10 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Arm type	Active comparator
Investigational medicinal product name	Elsiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage

10 mg/day elsiglutide.

Arm title	Elsiglutide 20 mg - additional population

Arm description:

Elsiglutide 20 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Arm type	Active comparator
Investigational medicinal product name	Elsiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 20 mg/day elsiglutide.

Arm title	Elsiglutide 40 mg - additional population

Arm description:

Elsiglutide 40 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Arm type	Active comparator
Investigational medicinal product name	Elsiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Elsiglutide was administered once daily as subcutaneous injection for 4 consecutive days at the dosage 40 mg/day elsiglutide.

Arm title	Placebo - additional population

Arm description:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

Number of subjects in period 1	Elsiglutide 10 mg - target population	Elsiglutide 20 mg - target population	Elsiglutide 40 mg - target population
Started	120	122	120
Completed	117	114	113
Not completed	3	8	7
Adverse event, serious fatal	-	1	2
Consent withdrawn by subject	2	3	3
Physician decision	1	1	-
subject did not receive study treatment	-	1	-
Adverse event, non-fatal	-	1	2
Other	-	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Placebo - target population	Elsiglutide 10 mg - additional population	Elsiglutide 20 mg - additional population
Started	123	4	4
Completed	112	4	3
Not completed	11	0	1
Adverse event, serious fatal	3	-	-
Consent withdrawn by subject	3	-	-
Physician decision	-	-	-
subject did not receive study treatment	-	-	-
Adverse event, non-fatal	2	-	1
Other	2	-	-
Lost to follow-up	1	-	-

Number of subjects in period 1	Elsiglutide 40 mg - additional population	Placebo - additional population
Started	3	2
Completed	2	2
Not completed	1	0
Adverse event, serious fatal	-	-
Consent withdrawn by subject	-	-
Physician decision	-	-
subject did not receive study treatment	-	-
Adverse event, non-fatal	1	-
Other	-	-
Lost to follow-up	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	498	498	
Age categorical Units: Subjects			
Age continuous Units: years median standard deviation	 61 ± 9.88	 -	
Gender categorical Units: Subjects			
Female	266	266	
Male	232	232	

Subject analysis sets

Subject analysis set title	FAS Target set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study medication (elsiglutide or placebo) and (at least part of) the chemotherapy regimen in Cycle 1. The FAS Target set was defined as all patients from the Target population who were eligible for the FAS.

Reporting group values	FAS Target set		
Number of subjects	484		
Age categorical Units: Subjects			
Age continuous Units: years median standard deviation	 61 ± 9.93	 	
Gender categorical Units: Subjects			
Female	258		
Male	226		

End points

End points reporting groups

Reporting group title	Elsiglutide 10 mg - target population

Reporting group description:

Elsiglutide 10 mg once daily as subcutanous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy

Reporting group title	Elsiglutide 20 mg - target population

Reporting group description:

Elsiglutide 20 mg once daily as s.c. injection for 4 consecutive days in patients receiving F-FU based chemotherapy.

Reporting group title	Elsiglutide 40 mg - target population

Reporting group description:

Elsiglutide 40 mg once daily as subcutanous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

Reporting group title	Placebo - target population

Reporting group description:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy.

Reporting group title	Elsiglutide 10 mg - additional population

Reporting group description:

Elsiglutide 10 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Reporting group title	Elsiglutide 20 mg - additional population

Reporting group description:

Elsiglutide 20 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Reporting group title	Elsiglutide 40 mg - additional population

Reporting group description:

Elsiglutide 40 mg once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Reporting group title	Placebo - additional population

Reporting group description:

Placebo once daily as subcutaneous injection for 4 consecutive days in patients receiving 5-FU based chemotherapy with monoclonal antibody.

Subject analysis set title	FAS Target set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study medication (elsiglutide or placebo) and (at least part of) the chemotherapy regimen in Cycle 1. The FAS Target set was defined as all patients from the Target population who were eligible for the FAS.

Primary: Proportion of Patients of the Target Population Experiencing a Maximum Grade ≥ 2 Diarrhea in Cycle 1 (Population: FAS Target Set)

End point title	Proportion of Patients of the Target Population Experiencing a Maximum Grade ≥ 2 Diarrhea in Cycle 1 (Population: FAS Target Set)[1]

End point description:

The endpoint of primary interest for efficacy was the proportion of patients within the Target population experiencing a maximum Grade ≥ 2 diarrhea in Cycle 1 (as assessed by the Investigator). For patient 8031362 who withdrew consent after 11 days in Cycle 1, Investigator assessments for the individual diarrhea events were missing.The data were imputed as Grade 0 for the primary endpoint, in line with the patient's eDiary data.
Grade of diarrhea according to NCI-CTCAE v 4.03 scale. Maximum grade: Maximum of the grades

assigned by the Investigator to the individual diarrhea events during the 14-day period.
p-value 2: Chi square test, with alpha = 0.10 (2-sided)
p-value 3 : Corrected for multiplicity according to Hommel's procedure Chi square test, with alpha = 0.10 (2 sided); this is the analysis used to test for treatment superiority

End point type	Primary

End point timeframe:

Cycle 1 was foreseen to last 14 days.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint of primary interest for efficacy was the proportion of patients within the Target population experiencing a maximum Grade ≥ 2 diarrhea in Cycle 1 (as assessed by the Investigator).

End point values	Elsiglutide 10 mg - target population	Elsiglutide 20 mg - target population	Elsiglutide 40 mg - target population	Placebo - target population
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	120	121[2]	120	123
Units: percentage				
number (not applicable)				
With maximum Grade ≥ 2 diarrhea	2.5	5	5.8	9.8
With maximum Grade < 2 diarrhea	97.5	95	94.2	90.2
p-value2 (comparison vs. placebo)	0.019	0.152	0.255	0
p-value2 (comparison vs. elsiglutide 10 mg)	0	0.314	0.196	0
p-value2 (comparison vs. elsiglutide 20 mg)	0	0	0.764	0
p-value3 (comparison vs. placebo)	0.113	0.455	0.51	0
p-value3 (comparison vs. elsiglutide 10 mg)	0	0.628	0.471	0
p-value3 (comparison vs. elsiglutide 20 mg)	0	0	0.764	0

Notes:

[2] - One subject was discontinued on the date of randomization and did not receive study treatment

Statistical analyses

Statistical analysis title	Chi square test

Statistical analysis description:

Overall null hypothesis: All elsiglutide dose groups had equal proportion of subjects with max Grade≥2 diarrhea and this was equal to the one in the placebo group. This includes 6 individual hypotheses (i.e., 3 to compare each dose group vs. placebo and 3 to compare dose groups vs. each other). Raw p-values from Chi square tests were corrected for multiplicity according to the Hommel's procedure. Each of 6 hypotheses was then evaluated based on corrected p-value at alpha 0.10 (two-sided).

Comparison groups	Elsiglutide 10 mg - target population v Elsiglutide 20 mg - target population v Elsiglutide 40 mg - target population v Placebo - target population
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.1 [4]
Method	Chi-squared

Notes:

[3] - The overall hypothesis system was represented by the following pool of partial hypothesis systems:
Hok: ⊓Gi = ⊓Gj i = 1 to 3, and j = 2 to 4, and k = 1 to 6, and i ≠ j
HAk: ⊓Gi ≠⊓Gj i = 1 to 3, and j = 2 to 4, and k = 1 to 6, and i ≠ j
where ⊓G is the probability of absence of Grade ≥2 CID for the Group.

Each Ho involved 2 groups.

[4] - Overall alpha level 0.10 was maintained by correction for multiplicity according to Hommel's procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

23 Jan 2015 to 09 Feb 2016

Adverse event reporting additional description:

The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day. SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set). Adverse events are reported for Cycles 1+2.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Elsiglutide 10 mg - SAF Overall set

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.
The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.
The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

Reporting group title	Elsiglutide 20 mg - SAF Overall set

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.
The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.
The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

Reporting group title	Elsiglutide 40 mg - SAF overall set

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.
The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.
The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

Reporting group title	Placebo - SAF overall set

Reporting group description:

Adverse events occurring during Cycle 1 + 2 are reported.
The safety (SAF) set was defined as all treated patients. "Patients treated" was defined as any patient who received any study medication (elsiglutide or placebo) on at least 1 day.
The SAF Overall set was defined as all patients who were part of the SAF (either of SAF Target set or of SAF Additional set).

Serious adverse events	Elsiglutide 10 mg - SAF Overall set	Elsiglutide 20 mg - SAF Overall set	Elsiglutide 40 mg - SAF overall set
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 124 (1.61%)	4 / 125 (3.20%)	3 / 123 (2.44%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events	0	0	0
Investigations			

Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 124 (0.00%)	1 / 125 (0.80%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 124 (0.00%)	1 / 125 (0.80%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Disease progression			

subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue inflammation			
subjects affected / exposed	0 / 124 (0.00%)	1 / 125 (0.80%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 125 (0.80%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 124 (0.81%)	1 / 125 (0.80%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 124 (0.81%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Septic shock			
subjects affected / exposed	1 / 124 (0.81%)	0 / 125 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Serious adverse events	Placebo - SAF overall set		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 125 (4.80%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Investigations			
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Supraventricular tachycardia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Soft tissue inflammation			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Abdominal abscess			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Elsiglutide 10 mg - SAF Overall set	Elsiglutide 20 mg - SAF Overall set	Elsiglutide 40 mg - SAF overall set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 124 (57.26%)	68 / 125 (54.40%)	73 / 123 (59.35%)
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 124 (4.84%)	7 / 125 (5.60%)	7 / 123 (5.69%)
occurrences (all)	6	8	9
Leukopenia			
subjects affected / exposed	6 / 124 (4.84%)	10 / 125 (8.00%)	6 / 123 (4.88%)
occurrences (all)	6	11	6
Neutropenia			
subjects affected / exposed	32 / 124 (25.81%)	29 / 125 (23.20%)	26 / 123 (21.14%)
occurrences (all)	44	34	34
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 124 (7.26%)	8 / 125 (6.40%)	7 / 123 (5.69%)
occurrences (all)	11	9	9
Injection site erythema			
subjects affected / exposed	1 / 124 (0.81%)	3 / 125 (2.40%)	10 / 123 (8.13%)
occurrences (all)	3	4	33

Gastrointestinal disorders			
Abdominal tenderness			
subjects affected / exposed	0 / 124 (0.00%)	11 / 125 (8.80%)	7 / 123 (5.69%)
occurrences (all)	0	37	17
Nausea			
subjects affected / exposed	21 / 124 (16.94%)	17 / 125 (13.60%)	15 / 123 (12.20%)
occurrences (all)	27	23	23
Vomiting			
subjects affected / exposed	1 / 124 (0.81%)	3 / 125 (2.40%)	7 / 123 (5.69%)
occurrences (all)	2	3	8

Non-serious adverse events	Placebo - SAF overall set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 125 (57.60%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 125 (7.20%)		
occurrences (all)	14		
Leukopenia			
subjects affected / exposed	12 / 125 (9.60%)		
occurrences (all)	13		
Neutropenia			
subjects affected / exposed	32 / 125 (25.60%)		
occurrences (all)	44		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	13		
Injection site erythema			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal tenderness			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	19		
Nausea			

subjects affected / exposed	17 / 125 (13.60%)		
occurrences (all)	23		
Vomiting			
subjects affected / exposed	5 / 125 (4.00%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2014	The protocol for this study was amended once. This amendment was implemented before the first patient was included in the study. Reasons for Amendment 1, dated 02 Dec 2014 were: • It was clarified that exclusion criteria 17 to 23 were to be checked on Day 1 of Cycle 1 as well as Day 1 of Cycle 2. • It was clarified that the Investigator is not kept blinded with regards to the patient's judgment about the occurrence of diarrhea. • The reporting of diarrhea events in the context of AE reporting was clarified. • It was defined that elsiglutide AEs included in the MedDRA high level term "injection site reactions" will be considered as AEs of special interest. • It was clarified that only IWRS, no Interactive Voice Response System was used in the study. • It was clarified that preventive measures against CID other than medications are permitted. • The nomenclature and use of documents was clarified for the Drug Preparation Form and the IWRS randomization confirmation e-mail. • It was clarified that urinalysis will not be restricted to dipstick analysis and that results for urine sample analysis did not have to be available for administration of study treatment on Day 1 to commence. • The description of the statistical analysis for QoL data and for vital signs data was corrected. • The Declaration of Helsinki was removed from the list of appendices and instead included in the list of references. • Administrative information and administrative changes: - The bioanalytical laboratory for citrulline testing and the company responsible for clinical trial supplies, packaging, and labelling were mentioned. - The contact details of sponsor representatives were adapted to show the actual address instead of a post-box address. • Minor text changes were implemented to clarify information, improve readability and remove incorrect or ambiguous wording.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported